52. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian total RNA extracted from plasma or serum, wherein the fraction comprises epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

53. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian RNA extracted from an acellular fraction of a bodily fluid, wherein the fraction comprising epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

Please cancel claims 11-20, 22-35, 38, 39, 42-45 and 47-50 without prejudice or disclaimer.

REMARKS

1. Status of the Claims

Claims 1, 2, 8-10, 36, 37, 21, 40, 41, and 51-53 as herein amended, and claims 3-7 and 46 as filed are pending in the application. The asserted grounds of rejection are overcome by amendment in part and traversed by argument in part.

Applicant appreciates the comments in the Office Action relating to the restriction requirement, and that the Sequence Listing is in compliance with 37 C.F.R. §1.821 *et seq*.

Applicant has acknowledges the objection to claims 7 and 8, and respectfully notes that the indefinite article "an" refers to the method and not the RNA.

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Reconsideration of this objection is requested.

2. The amended claims fulfill the requirements of 35 U.S.C. §112.

Claim 21 stands rejected under 35 U.S.C. §112, second paragraph for indefiniteness. The claim is deemed vague and indefinite due to claim structure. Applicant has amended claim 21 to overcome this rejection, and requests that it be withdrawn.

3. The amended claims are non-obvious over the cited prior art.

Claims 1-12, 21, 36, 37, 40, 41, 52 and 53 stand rejected under 35 U.S.C. §103 as being obvious over the teachings of Kopreski *et al.* in view of the teachings of Leitzel *et al.* Applicants respectfully traverse.

The primary reference cited in this rejection, Kopreski *et al.*, is available as a reference solely because the Patent Office has not recognized Applicant's priority claim to related U.S. provisional application Serial No. 60/014,730, International Application No. PCT/US97/03479, and U.S. Patent No. 6,329,179. The Action asserts that these priority applications did not teach epidermal growth factor receptor.

On the contrary, these references explicitly teach epidermal growth factor receptor, albeit under the name "erb-B-1" (see, for example, col. 11, line 23 of the '179 patent). This is an accepted abbreviation for this receptor, as evidenced by Schlegel *et al.* (1994, *Int J Cancer* 56: 72-77, previously submitted in Applicant's Information Disclosure Statement and considered by the Examiner), first paragraph first page, which states:

> "The epidermal-growth factor (EGF) receptor is a transmembrane glycoprotein...The EGF receptor gene *c-erbB* has been cloned...."(italics added).

Further, this synonymous terminology is explicitly clarified by the inventor in the instant at page 3, lines 7-9:

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"US Patent Application Serial No. 09/155,152, incorporated by reference herein in its entirety, further taught that tumor-associated or tumor-derived RNAs include erb-B-1 mRNA (also known as epidermal growth factor receptor mRNA)...(emphasis added).

Additionally, epidermal growth factor receptor RNA was further taught in the '179 patent, as well as the aforesaid PCT and provisional applications, under the provided Case 4, wherein it is taught that a multiplex panel for serum RNA may advantageously include "myc, ras, P53, EGFr, and Her-2-neu RNA (col. 20, l. 23-24, emphasis added). It is well recognized in the art that "EGFr RNA" refers to epidermal growth factor receptor RNA (see, for example, previously-cited Schlegel *et al.* and LeRiche *et al.* (1996, *J. Clin. Endocrinol. Metab.* 81: 656-662, also previously provided), in title and second paragraph thereof, and also Dahiya et al (1996, *Urology* 48: 963-970, previously provided) in the abstract thereof. Both of these prior art citations reference epidermal growth factor receptor as EGF-R.

In order to avoid even the appearance of confusion on this point, Applicant has amended the pending claims to recite the abbreviation in the claim, to provide explicit and unambiguous support from the specification for these claims.

Applicant thus respectfully requests that the Office acknowledge the appropriate priority date for disclosure and claims relating to epidermal growth factor receptor as the filing date of US Serial No. 60/014,730, filed on March 26, 1996, in view of the evidence set forth herein.

Once the appropriate priority date is recognized, neither the primary reference, Kopreski *et al.*, nor the secondary reference, Leitzel *et al.* is no longer prior art. Leitzel *et al.* is in any event not sufficient support for this ground of rejection. The Leitzel reference is acknowledged to teach detection of cancer *cells* in peripheral blood that express the epidermal growth factor receptor. The Action further acknowledges that there is *no* teaching, suggestion or motivation in the Leitzel reference to detect epidermal growth factor RNA is blood plasma or serum, or in an acellular fraction of a bodily fluid, since the reference is explicitly directed to detecting *intracellular* RNA. Standing alone, the Leitzel reference cannot support a prima facie case of obviousness

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against the rejected claims. Accordingly, Applicant respectfully requests that the Office withdraw this ground of rejection.

Claims 46 and 51 stand rejected under 35 U.S.C. §103 as being obvious over the teachings of Zhou *et al.* in view of the teachings of Emanuel *et al.* Claims 46 and 51 also stand rejected under 35 U.S.C. §103 as being obvious over the teachings of Burd *et al.* in view of the teachings of Emanuel *et al.* Applicants respectfully traverse.

Applicant notes that the basis for each of these grounds of rejection are that the prior art taught generically the concept of diagnostic kits (Emanuel *et al.*), and the other cited references taught the particular genes recited in the claims. Applicant respectfully submits that the diagnostic kits are distinguishable over the cited prior art. Contrary to the assertions in the Office Action, the skilled artisan would *not* have had any expectation of successfully using a diagnostic kit in the prior art to amplify or otherwise detect gene-specific RNA from blood plasma or serum, or from an acellular fraction of a bodily fluid, because the art explicitly taught that such RNA could not be isolated using whatever reagents or other components were available.

Indeed, it was "well known" in the art that RNA is rapidly degraded by serum ribonucleases. Two prior art references are sufficient to demonstrate this point: Komeda *et al.* (1995, *Cancer* 75: 2214-2219) and Pfleiderer (1995, *Int. J. Cancer* 64: 135-139). Applicant has previously provided both references, however, they are appended hereto for the Examiner's convenience.

The Komeda reference teaches that one aim of the reported study was "[t]o examine whether free mRNA in blood could also be detected" (p.2215), and further states that "[i]t was *impossible* to detect free RNA extracted from Hep G2 cells when they were diluted once with control blood" (p.2216; *emphasis added*), using RNA isolation and RT-PCR amplification methods substantially similar to the methods taught in the cited references. Pfleiderer, who also used RT-PCR amplification methods, teaches that the author "tested whether free . . . RNA in peripheral blood would also be detected . . .. As shown in figure 2, even high

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concentrations of . . . RNA (corresponding to 1% tumour cells) in peripheral blood were not detectable . . . indicated rapid and complete removal of free . . . RNA . . . by degradation . . ." (p.136). Further, the reference states that ". . . intact tumour cells are the *only* source of positive RT-PCR results. Free tumour RNA in blood, which might be released from cells . . . was not sufficiently stable to be detected . . ." (p. 137; *emphasis added*).

Applicant respectfully contends that these references demonstrate that one of ordinary skill would not have believed that any diagnostic kit could be made according to the cited references that could detect RNA in blood plasma or serum, or from an acellular fraction of a bodily fluid. Thus, Applicant respectfully contends that the cited prior art is insufficient to support a prima facie obviousness rejection, and requests that the Patent Office withdraw these grounds of rejection.

Applicant believing that all grounds of rejection have been overcome by amendment or traversed by argument, he respectfully solicits the Patent Office to withdraw these grounds of rejection.

4. **The claims are not obvious under the judicially-created obviousness-type double patenting doctrine.**

Claims 1, 2, 6-8, 15 and 81-83 stand rejected under the judicially-created doctrine of obviousness-type double patenting, based on the disclosure of U.S. Patent No. 6,329,179. Applicants submit herewith an appropriate terminal disclaimer, which overcomes rejection on obviousness-type double patenting grounds.

CONCLUSION

Applicants believe that all requirements of patentability have been fully met, and allowance of the claims is respectfully solicited.

If the Examiner in charge of this application believes it to be helpful, he is invited to contact the undersigned attorney by telephone at (312) 913-0001.

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Respectfully submitted,
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"Marked-up" copy of amended claims

1. (Amended) A method for detecting tumor-derived or tumor-associated RNA in the plasma or serum fraction of blood from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:

a) extracting mammalian total RNA from plasma or serum, wherein a fraction of said extracted RNA comprises a tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA prepared therefrom, wherein amplification is performed [in] either [a] qualitatively or quantitatively [fashion] using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and

c) detecting the amplified product produced from the RNA or cDNA.

2. (Amended) A method for detecting extracellular tumor-derived or tumor-associated RNA in a non-cellular fraction of a bodily fluid from a human or animal, wherein the tumor-derived or tumor-associated RNA is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of:

a) extracting mammalian total RNA from a non-cellular fraction of a bodily fluid, wherein a fraction of said extracted RNA comprises an extracellular tumor-derived or tumor-specific RNA species that is epidermal growth factor RNA, epidermal growth

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factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or cDNA corresponding thereto, wherein amplification is performed [in] either [a] qualitatively or quantitatively [fashion] using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and

c) detecting the amplified product produced from the RNA or cDNA corresponding thereto.

8. (Amended) The method of claim 2, wherein the RNA in step (a) is extracted from a non-cellular fraction of a bodily fluid using an RNA extraction method that is a gelatin extraction method; silica, glass bead, or diatom extraction method; guanidine-thiocyanate-phenol solution extraction method; guanidinium thiocyanate acid-based extraction method; phenol-chloroform-based extraction method; or involves centrifugation through a cesium chloride or similar gradient.

9. (Amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the steps of performing the method of claim 1 qualitatively or quantitatively, and detecting a product produced by said RNA in the plasma or serum of said animal or human, wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.

10. (Amended) The method for screening an animal or human for malignancy or premalignancy associated with epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, the method comprising the

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steps of performing the method of claim 2 qualitatively or quantitatively, and detecting a product produced by said RNA in the plasma or serum of said animal or human, wherein detection of said RNA indicates that malignant or premalignant cells are present in the body of said animal or human.

21. (Amended) A method for monitoring an animal or human for a malignant or premalignant disease, wherein the malignant or premalignant disease is associated with a tumor-derived or tumor-associated RNA that is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, the method comprising the step of:

[1) detecting RNA associated with the malignant or premalignant disease qualitatively or quantitatively , wherein the RNA is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof, according to a method comprising the steps of:]

a) extracting mammalian total RNA from plasma or serum, wherein a fraction of said extracted RNA comprises epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or corresponding cDNA, wherein amplification is performed qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto, to produce an amplified product; and

c) detecting the amplified product produced from RNA or cDNA corresponding thereto.

36. (Amended) A method for selecting an animal or human with cancer for a cancer-directed therapy, the method comprising the steps of:

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a) extracting mammalian total RNA from plasma or serum of the animal or human, wherein a fraction of said extracted RNA comprises a tumor-derived or tumor-specific RNA that is epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, or heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof;

b) amplifying or signal amplifying said fraction of the extracted RNA or cDNA corresponding thereto, wherein amplification is performed qualitatively or quantitatively using primers or probes specific for the tumor-derived or tumor-associated RNA or cDNA corresponding thereto to produce an amplified product; and

c) detecting the amplified product produced from said RNA or cDNA, whereby detection thereof selects the human with cancer for a cancer directed therapy.

37. (Amended) A method according to claim 1, further comprising the step of performing a diagnostic test for diagnosing cancer or premalignancy when epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof is detected in plasma or serum of an animal or human.

40. (Amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 on blood plasma or serum from an animal or human with cancer to whom anticancer therapy is administered, and wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

41. (Amended) A method for monitoring response to an anticancer therapy, comprising the step of performing the method of claim 1 on blood plasma or serum from an animal or human with cancer to whom anticancer therapy is administered, and

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wherein response to the anticancer therapy is accomplished by qualitative or quantitative detection of epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA or any combination thereof.

51. (Amended) A diagnostic kit comprising primers specific for amplifying heterogeneous nuclear ribonucleoprotein A2/B1 RNA or cDNA prepared therefrom and reagents for extracting total RNA from an acellular fraction of a bodily fluid according to the method of claim 2.

52. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian total RNA extracted from plasma or serum, wherein the fraction comprises epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

53. (Amended) A method for producing cDNA by reverse transcription of a fraction of extracellular mammalian RNA extracted from an acellular fraction of a bodily fluid, wherein the fraction comprising epidermal growth factor RNA, epidermal growth factor receptor (erb-B-1) RNA, her-2/neu RNA, c-myc RNA, heterogeneous nuclear ribonucleoprotein A2/B1 RNA, or any combination thereof, whereby cDNA corresponding to said RNA is produced.

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